transcription of a gene sequence, *i.e.*, a transcription-activating protein. "Transcription-activating" is a term used to refer to characteristics of a protein that promote transcription. As used herein, a transcription-activating protein would include proteins that increase accessibility of the DNA to transcription complexes, for example, by opening or relaxing chromatin structure, proteins that promote the recognition and/or binding of transcription complexes to a target gene sequence, and/or proteins that promote transcription complex movement along the length of the template DNA sequence.

Regulatory proteins of secondary metabolite production and the nucleic acid sequences encoding these are known to those skilled in the art. Non-limiting examples of regulatory proteins of secondary metabolite synthesis include: regulator proteins of the aflatoxin/sterigmatocystin biosynthetic cluster (Woloshuk, C.P., *et al.*, *Appl, Environ. Microbiol.* **60**:2408-2414 (1994) and Brown, D.W., *et al.*, *Proc Natl Acad Sci U S A.* **93**:1418-1422 (1996)); regulator proteins of the paxilline biosynthetic cluster (Young, C., *et al.*, *Mol, Microbiol.* **39**:754-764 (2001)); regulator proteins of the cephalosporin and penicillin biosynthetic clusters (Litzka O., *et al.*, *Antonie Van Leeuwenhoek* **75**:95-105 (1999); Schmitt E.K. and Kuck U., *J. Biol. Chem.* **275**:9348-9357 (2000); MacCabe *et al. Mol. Gen. Genet.* **250**:367-374 (1996); Suarez *et al. Mol. Microbiol.* **20**:529-540 (1996); Lambert *et al. Mol. Cell. Biol.* **17**:3966-3976 (1997); Su *et al. Genetics* **133**:67-77 (1993); regulator proteins of tricothecene synthesis (Trapp S.C., *et al.*, *Mol. Gen. Genet.* **257**:421-432 (1998); Brown D.W., *et al.*, *Fungal Genet. Biol.* **32**:121-133 (2001); and Matsumoto G., *et al. Biosci. Biotechnol. Biochem.* **63**:2001-2004 (1999)); and regulator proteins of lovastatin synthesis (Kennedy, J., *et al.*, *Science* **284**:1368-1372 (1999); Hendrickson *et al.*, *Chem. Biol.* **6**:429-439 (1999) Tag, A. *et al.*, *Mol Microbiol.* **38**:658-65 (2000)).

Certain embodiments of the aspects of the invention disclosed herein relate to the lovE regulator protein, a protein which plays a key role in the biosynthesis of lovastatin. More particularly, certain embodiments of the aspects of the invention relate to variant proteins of the lovE regulator protein and methods of making the same. Such proteins are variant with respect to the following *A. terreus* wild-type *lovE* sequences (SEQ ID NOS:91 and 92).

Table 1: Amino Acid and Nucleic Acid Sequences of Wild-type *lovE*

***Wild-type lovE* Amino Acid Sequence**

maadqgiftnsvtlspvegsrtggtlprrafrrscdrchaqkikctgnkevtgrapcqrc
qqaglrcvysercpkrklrqsraadlvsadpdpclhmssppvpsqslpldvseshssnts
rqfldppdsydwswtsigtdeaidtdcwglsqcdggfscqleptlpdlpspfestvekap
lppvssdiaraasaqrelfddlsavsqeleeillavtvewpkqeiwthpigmffnasrrl
ltvlrqqaqadchqgtldeclrtknlftavhcyilnvriltaiselllsqirrtqnshms
plegsrsqspsrddtsssghssvdtipffsenlpigelfsyvdplthalfsacttlhvg
vqllreneitlgvhsaqgiaasismsgepgediartgatnsarceeqpttpaarvlfmfl
sdegafqeaksagsrgrtiaalrrcyedifslarkhkhgmlrdlnnipp (SEQ ID NO:91)

Wild-type lovE DNA Sequence

atggctgcagatcaaggtatattcacgaactcggtcactctctcgccagtggagggttca
cgcaccggtggaacattaccccgccgtgcattccgacgctcttgtgatcggtgtcatgca
caaaagatcaaatgtactggaaataaggaggttactggccgtgctccctgtcagcgttgc
cagcaggctggacttcgatgcgtctacagtgagcgatgccccaagcgcaagctacgccaa
tccagggcagcggatctcgtctctgctgacccagatccctgcttgcacatgtcctcgcct
ccagtgccctcacagagcttgccgctagacgtatccgagtcgcattcctcaaatacctcc
cggcaatttcttgatccaccggacagctacgactggtcgtggacctcgattggcactgac
gaggctattgacactgactgctgggggctgtcccaatgtgatggaggcttcagctgtcag
ttagagccaacgctgccggatctaccttcgcccttcgagtctacggttgaaaaagctccg
ttgccaccggtatcgagcgacattgctcgtgcggccagtgcgcaacgagagcttttcgat
gacctgtcggcggtgtcgcaggaactggaagagatccttctggccgtgacggtagaatgg
ccgaagcaggaaatctggacccatcccatcggaatgtttttcaatgcgtcacgacggctt
cttactgtcctgcgccaacaagcgcaggccgactgccatcaaggcacactagacgaatgt
ttacggaccaagaacctctttacggcagtacactgttacatattgaatgtgcggattttg
accgccatatcggagttgctcctgtcgcaaattaggcggacccagaacagccatatgagc
ccactggaagggagtcgatcccagtcgccgagcagagacgacaccagcagcagcagcggc
cacagcagtgttgacaccataccttctttagcgagaacctccctattggtgagctgttc
tcctatgttgacccccctgacacacgccctattctcggcttgcactacgttacatgttggg
gtacaattgctgcgtgagaatgagattactctgggagtacactccgcccagggcattgca
gcttccatcagcatgagcggggaaccaggcgaggatatagccaggacaggggcgaccaat
tccgcaagatgcgaggagcagccgaccactccagcggctcgggttttgttcatgttcttg
agtgatgaaggggctttccaggaggcaaagtctgctggttcccgaggtcgaaccatcgca
gcactgcgacgatgctatgaggatatcttttccctcgcccgcaaacacaaacatggcatg
ctcagagacctcaacaatattcctccatga (SEQ ID NO:92)

As used herein, the term "secondary metabolite" means a compound, derived from primary metabolites, that is produced by an organism, is not a primary metabolite, is not ethanol or a fusel alcohol, and is not required for growth under standard conditions. Secondary metabolites

are derived from intermediates of many pathways of primary metabolism. These pathways include, without limitation, pathways for biosynthesis of amino acids, the shikimic acid pathway for biosynthesis of aromatic amino acids, the polyketide biosynthetic pathway from acetyl coenzyme A (CoA), the mevalonic acid pathway from acetyl CoA, and pathways for biosynthesis of polysaccharides and peptidopolysaccharides. Collectively, secondary metabolism involves all primary pathways of carbon metabolism. Particularly preferred in embodiments of the aspects of the invention are fungal secondary metabolites (*See*, Fungal Physiology, Chapter 9 (Secondary(Special) Metabolism), Griffin, D. H., John Wiley & Sons, Inc.; ISBN: 0471166154).

"Secondary metabolite" also includes intermediate compounds in the biosynthetic pathway for a secondary metabolite that are dedicated to the pathway for synthesis of the secondary metabolite. "Dedicated to the pathway for synthesis of the secondary metabolite" means that once the intermediate is synthesized by the cell, the cell will not convert the intermediate to a primary metabolite. "Intermediate compounds" also include secondary metabolite intermediate compounds which can be converted to useful compounds by subsequent chemical conversion or subsequent biotransformation. As such, providing improved availability of such intermediate compounds would still lead to improved production of the ultimate useful compound, which itself may be referred to herein as a secondary metabolite. The yeast *Saccharomyces cerevisiae* is not known to produce secondary metabolites.

The term "primary metabolite" means a natural product that has an obvious role in the functioning of almost all organisms. Primary metabolites include, without limitation, compounds involved in the biosynthesis of lipids, carbohydrates, proteins, and nucleic acids. The term "increasing the yield of the secondary metabolite" means increasing the quantity of the secondary metabolite present in the total fermentation broth per unit volume of fermentation broth or culture.